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Rationale and methodology of monitoring ambulatory blood pressure and arterial compliance in the Hypertension in the Very Elderly Trial

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Objective This article describes the rationale and methodology for the monitoring of ambulatory blood pressure and arterial compliance in hypertensive patients aged 80 years and above. This is a side project of the Hypertension in the Very Elderly Trial.

Methods The hypertension in the Very Elderly Trial is a multicentre, double-blind, randomized, placebo-controlled trial aiming to investigate the effect of active treatment on cardiovascular and other outcomes in hypertensive patients aged 80 years or more. Patients are randomized to placebo or active treatment starting with the diuretic indapamide and adding the angiotensin-converting enzyme inhibitor perindopril if required. This study has completed a pilot trial and the main trial is now underway. Six hundred patients will have two ABPM recordings, the first at baseline and the second a year after randomization. Arterial compliance is measured using the Q wave (electrocardiogram) to Korotkoff diastole sound interval.

Results Baseline characteristics for the first 50 patients recruited are presented.

Conclusion This side project will allow the investigation of 24-h ambulatory measures of blood pressure and arterial compliance as predictors of cerebrovascular and cardiovascular events in the very elderly. The project will also allow the investigation of the blood pressure and vascular compliance profiles in the very elderly and their changes with posture. The association between these measurements and mortality and morbidity in this age group will be addressed. *Blood Press Monit* 11:3–8

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Introduction

It is very important to measure ambulatory blood pressure in a long-term clinical trial such as the Hypertension in the Very Elderly Trial (HYVET). Blood pressure, particularly systolic pressure, is highly variable and its degree of variability increases with age [1]. The single sphygmomanometric recording of blood pressure in outpatients does not reflect the variability in blood pressure. It is possible that both the level of and variability in blood pressure will contribute to morbidity and mortality in the very elderly. Moreover, ambulatory blood pressure recordings from the Systolic Hypertension in Europe (Syst-Eur) Trial showed that ambulatory blood pressure was a better predictor of mortality and morbidity than clinic systolic and diastolic pressure [2]. The discrepancy between clinic and 24-h ambulatory blood pressure increases with age [3], making it important to assess ambulatory blood pressure in individuals over the age of 80 years. Given the increase in systolic blood pressure with age and the levelling of diastolic blood pressure over the age of 60 years, pulse pressure also increases and the implications of this need to be assessed.

Postural hypotension is also a major problem in the very elderly [4]. This can be exaggerated after prolonged rest, in the postprandial period and after use of certain antihypertensive medications [5–7]. If postural hypotension is severe, it results in postural symptoms that can be associated with falls [8]. This may result in a proportion of these cases having considerable long-term morbidity and also possible mortality. The variability of blood pressure measurements during the day is expected to reflect postural and postprandial hypotension. The postural effect will be directly measured during the study and the postprandial effect deduced from the time of day.

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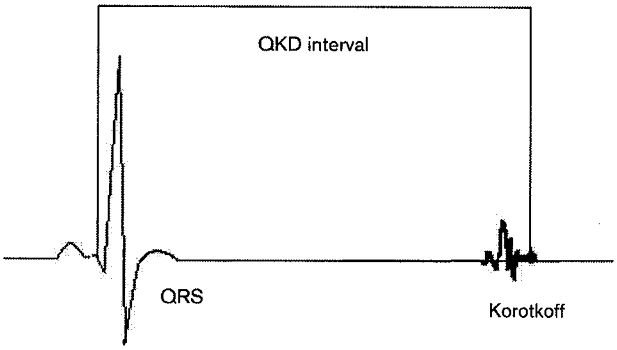
Fig. 1



The QKD is the time interval between the Q wave of the electrocardiogram and the disappearance of the Korotkoff sounds in the brachial artery in diastole.

Arterial compliance is defined as a change in arterial volume following a change in pressure. Increase in arterial stiffness and the consequent decrease in arterial compliance has emerged in the last decade as an independent cardiovascular and cerebrovascular risk factor [9–12]. We are taking the opportunity to measure ambulatory arterial compliance in HYVET.

The direct measurement of arterial compliance is difficult; our preferred method to measure arterial compliance is pulse wave velocity. Pulse wave velocity is determined by dividing the distance travelled by a pulse wave by the time taken to travel this distance, the pulse interval. This is expressed in metres per second. A number of limitations to this method, have been found, however. It is an indirect measurement that is inversely related to arterial compliance. QKD is an estimation of arterial compliance, including both the pulse interval between the left ventricle and the brachial artery and also the ventricular ejection time. As the ventricular ejection time may be related to aortic compliance, the QKD is possibly a more relevant estimate of aortic compliance, but this has yet to be proven. QKD is the time interval, in milliseconds, between the Q wave [electrocardiogram (ECG) signal] and the Korotkoff V (K) sound at the brachial artery in diastole (D) (Fig. 1). This measure of arterial compliance involves the central aorta and brachial artery and is decreased in hypertension. The QKD interval has been shown to relate closely to ageing [13].

Methods

HYVET is a large international multicentred trial designed to study the benefits of antihypertensive therapy in the very elderly (aged 80 years or more) [14,15]. Patients are randomized to placebo or active treatment starting with the diuretic indapamide (slow release 1.5 mg) and adding the angiotensin-converting enzyme inhibitor perindopril (2–4 mg), as required. This study has completed a pilot trial [16] and the main trial is now underway.

In order to answer important questions regarding the prognostic value of ambulatory blood pressure and arterial compliance in the very elderly, this side project of HYVET was initiated. The project will also allow the investigation of the blood pressure and compliance profile in the very elderly and their changes with posture. The possible association between these measurements and mortality and morbidity in this age group will be addressed.

The following hypotheses are tested in this side project:

Primary hypotheses

(1) Whether ambulatory blood pressure recordings in the elderly are a better predictor of cerebrovascular and cardiovascular end points than clinic pressures.
(2) Does arterial compliance, as measured by QKD, have a direct relationship with total mortality or cardiovascular and cerebrovascular events?

Secondary hypotheses

(1) Whether pulse pressure in the very elderly is a better predictor of mortality or morbidity than systolic or diastolic pressure.
(2) Whether blood pressure variability is a predictor of cerebrovascular or cardiovascular end points.
(3) Do the active treatments employed in the HYVET alter arterial compliance?

All the main HYVET centres are invited to participate in this side project on ambulatory blood pressure recording and arterial compliance. The entry criteria for this side project are the inclusion and exclusion criteria for the main HYVET trial [14,15]. Following an amendment to the protocol, patients with isolated systolic hypertension were also recruited. Patients are excluded from this side project if they are unable to keep the blood pressure monitor on for 24 h because of any physical impairment or any physical disability. Centres are encouraged to enrol all their patients in this side project.

The recorder employed is the Diasys Integra II ambulatory blood pressure monitoring system (Novacor – S.A., Rueil, France). This machine is a validated ambulatory monitoring device [17,18] and has been used in a number of trials [12,19–21].

The Diasys Integra system comprises the recorder, a cuff with double air/electric tubing for connection to the

Diasys monitor and an ECG cable with a position sensor. A microphone, enclosed within the cuff and placed over the patient's brachial artery, allows for the detection of Korotkoff sounds. The single-channel ECG cable and position sensor records the patient's position and also allows for ECG gating.

The Diasys Integra II has two standard modes of operating, the auscultatory mode and the oscillometric default mode. The former uses the ECG gating and the disappearance of the Korotkoff sounds in diastole, to calculate the QKD interval. The oscillometric mode of taking blood pressure is based on the relationship between the oscillometric curve and the curve of cuff pressure, and so the QKD is not determined. At the beginning of each monitoring, the Diasys runs two test measurements. If the quality of the Korotkoff sounds is adequate, the monitor operates in auscultatory mode. The oscillometric mode is selected on occasions when the Korotkoff sounds cannot be detected. If the monitor is set up as per intent, it should provide 39 readings in a 24-h period.

Patients who participate in this side project will undergo an initial 24-h ambulatory blood pressure recording before randomization and while on placebo. A second ambulatory blood pressure recording will be taken 12 months later.

The Diasys Integra II is programmed so that the blood pressure and QKD are recorded every 30 min between 07:00 and 22:00 h and hourly between 22:00 and 07:00 h. The patient's position, lying or standing, is registered at each recording.

Software and statistical considerations

Data acquired by the Diasys monitor is transferred to a PC through the data transfer port using the NovaDrive software (Novacor – S.A.). The downloaded ASCII files are then sent to the coordinating office (Care of the Elderly, Imperial College London, London, UK) via e-mail. The data received are processed using the DiasySoft software (Novacor – S.A.). In addition, a copy of the results is sent back to the investigator for their record. For statistical analysis, the results are exported as an excel spreadsheet onto an SAS database.

The ability of office and ambulatory pressures to predict mortality will be compared by the calculation of the sensitivity and specificity of a range of both office and ambulatory pressures. These results will be employed to construct receiver–operator characteristic curves, the areas under which will be compared statistically. For a death rate of 24%, 600 individuals would detect a difference between two receiver–operator characteristic curves of 0.1 at the 1% level of significance and a power of 90% (R. Newson, personal communication).

Results

The baseline daytime blood pressure characteristics of the first 50 patients, recruited while on placebo, are presented in Table 1.

An amendment to the original protocol was carried out allowing recruitment of patients with isolated systolic hypertension. According to the original protocol, patients were eligible for the trial if they have a sustained systolic pressure while on placebo of 160–199 mmHg, and at the same time, a diastolic (phase V) pressure 90–109 mmHg. After the amendment, patients are eligible for the trial if they have a sustained systolic pressure while on single-blind placebo of 160–199 mmHg, and at the same time, a diastolic (phase V) pressure of < 110 mmHg. The clinic blood pressures, on placebo, averaged 37/7 mmHg higher than the daytime ambulatory pressure for isolated systolic hypertension patients and 41/17 mmHg for those with combined systolic and diastolic hypertension.

Discussion

Our results have shown a considerable difference between the clinic blood pressures and the ambulatory measurements. Previous studies were conducted with younger hypertensive patients [2] and the very old nonhypertensive individuals [22,23]. In both these studies, the difference between ambulatory and clinic blood pressure was lower than that in the HYVET study. It is known that the difference between ambulatory and clinic measures increases with age and also with hypertension. This could explain the large difference we found in our group of very elderly hypertensive patients. This difference, however, will have to be confirmed as a larger number of participants enter the trial.

The results of this study will further our understanding of the pathophysiology of hypertension as it applies to the

Table 1 Average results for both patients with ISH and combined systolic and diastolic hypertension

					Daytime			
	Office systolic BP		Office diastolic BP		Ambulatory systolic BP		Ambulatory diastolic BP	
	mmHg	SD	mmHg	SD	mmHg	SD	mmHg	SD
ISH patients ($n=16$)	176	9.8	83	4.6	139	13.2	76	10.4
Non-ISH patients ($n=34$)	173	9.1	95	3.9	132	15.4	78	10.7
All patients ($n=50$)	174	9.4	91	6.9	134	14.9	77	10.5

ISH, isolated systolic hypertension; BP, blood pressure.

very elderly. From a practical point of view, this study will help medical personnel to take decisions regarding whether to treat hypertension in the very elderly according to the level of both clinical and ambulatory blood pressure. Staessen *et al.* [24] showed that in younger patients, the adjustment of antihypertensive treatment, on the basis of ambulatory blood pressure monitoring instead of clinic blood pressure measurements, led to a reduced drug treatment for the same level of blood pressure control .

A review by Staessen and coworkers for the 2001 Consensus Conference on Ambulatory Blood Pressure Monitoring defined white-coat hypertension as blood pressure consistently equal to or higher than 140/90 when the average ambulatory blood pressure is below 135/85. The side project to the Syst-Eur Trial has found that the favourable effect of antihypertensive treatment was only detected in patients with sustained hypertension, as measured by ambulatory blood pressure, and not in those with nonsustained hypertension. They also concluded that ambulatory blood pressure monitoring significantly refined the prediction of cardiovascular events when compared with conventional blood pressure measurements [25,26]. In the case of very elderly patients (≥ 80 years), no studies have been carried out so far to determine the cardiovascular and cerebrovascular prognostic efficacy of ambulatory blood pressure monitoring.

The present study will also address the variability of blood pressure in the very elderly and this may help either to modify treatment or the timing of drug therapy in patients over 80 years of age. Cardiovascular risks factors such as old age or diabetes are associated with a higher short-term variability in blood pressure, and intermittent measurements could miss this variability. Several studies have shown that both decreased and exaggerated nighttime dipping lead to a worse prognosis [27,28]; however, the importance of this in the very elderly is not known. The automatic detection of postural position used in this study may clarify the importance of the nocturnal dip by ensuring that nocturnal pressures are measured with the patient supine.

The population size of 600 patients is considered to be sufficient to test the hypotheses described above. Considerable experience in ambulatory pressure monitoring was gained during the Syst-Eur Trial carried out in elderly patients (mean age 71 years) with isolated systolic hypertension [29]. In that trial, it was reported that a population size of 80 participants was sufficient to detect an average BP fall of 9/5 mmHg [29]. Moreover, 695 patients were sufficient to examine the differences between clinic and ambulatory measurements [26]. As the clinic ambulatory differences are exaggerated with increasing age [2], 600 patients are considered adequate for the present study.

Liang and coworkers [30] described a study using pulse wave velocity and other measures of arterial compliance to determine repeatability and appropriate sample size required to determine treatment differences. A population size of 50 individuals was found to be appropriate to find a 10% variation in pulse wave velocity.

Arterial pulse wave velocity is a measure of arterial compliance or 'elasticity', and can be measured noninvasively [30]. Stiffening of the large arteries results in higher pulse wave velocities and an increase in both systolic and pulse pressure with a lowering of diastolic pressure. This may decrease coronary perfusion, and ultimately the cardiac workload is increased in the face of reduced coronary perfusion [11]. Arterial compliance declines with ageing and hypertension [31,32], and is also reduced in the presence of diabetes, cardiovascular and cerebrovascular disease [9,11,33–35]. An increase in arterial stiffness with age, predominantly in elastic arteries, has been established in various studies [36]. Exercise training, hormone replacement therapy in women and antihypertensive medication increase arterial compliance [32,37–39]. Although there are no prospective studies at present to show the relationship between arterial compliance and mortality, there are, however, many studies showing that low arterial compliance is related to completed strokes and myocardial infarction [9–11]. Arterial compliance is, therefore, increasingly regarded as a modifiable risk factor for coronary heart disease, and attempts to modify it may have to be addressed seriously. The use of arterial compliance to estimate mortality and morbidity in the very elderly is not established. This study will allow the determination of diurnal (24-h) variations in arterial compliance and its implications for morbidity and mortality.

The QKD is a simple and convenient measure of arterial compliance and is recorded in conjunction with ambulatory blood pressure. The QKD measures the reduced distensibility by measuring the time related to the pulse wave velocity over an area of large elastic arteries, especially the aorta. This has a role in the increased cardiovascular risk that occurs in response to diabetes, renal failure, ageing or hypertension. The 24-h ambulatory measures may be very useful as they measure the variation in compliance in relationship to variations in blood pressure and heart rate. Gosse and coworkers [40] described a correlation between mean QKD and age, height, mean 24-h systolic blood pressure and heart rate, and fractional shortening. The advantage of QKD compared with other measures is that it is measured simultaneously with blood pressure, in the same instrument, and is independent of white-coat effect or observer bias [40]. QKD has been reported to be a good measure to determine the impact of age on arterial compliance [13]. In addition, it has also been found to be a reproducible method in previous studies [41].

Pulse pressure is a surrogate measure of arterial compliance. Alderman and coworkers [42] reported, in a 20-year follow up study, that after adjusting for other variables, pulse pressure was a significant predictor of cardiovascular events in patients following antihypertensive therapy. A meta-analysis pooled from the results obtained in the European Working Party on High Blood Pressure in the Elderly, the Syst-Eur and the Syst-China Trial, has shown that Pulse pressure was a better determinant of myocardial infarction and cardiovascular risks in the elderly than systolic blood pressure [43]. The Syst-Eur Trial also demonstrated that ambulatory pulse pressure was a better predictor of cardiovascular events than clinic pulse pressure in older patients [44]. In the present study, the relative risk of 24-h, diurnal and nocturnal pulse pressure will be determined in relation to mortality and will be compared with the clinical measurements to determine relative risk.

Conclusions

The results obtained will help clinicians to make informed decisions regarding the treatment of the very elderly hypertensive patients.

The value of ambulatory blood pressure and arterial compliance in the very elderly as predictors of mortality and morbidity will be evaluated.

The project will also allow the investigation of the blood pressure and compliance profile in the very elderly, and their changes with posture and meal times. The possible association between these measurements and mortality and morbidity in this age group will be addressed.

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